REMARKS/ARGUMENTS

Applicants respond to the Examiner's remarks using the paragraph numbering of the office action.

2. Applicants have updated the cross-reference to related applications as requested.

8. A set of 47 replacement sheets of formal drawings are attached. The drawings have been amended to comply with standards for margins and font size as defined under 37 CFR 1.84(g) and 37 CFR 1.84(p)(3). These amendments contain no new matter.

9. Applicants have corrected a number of typographical errors in the specification. These amendments contain no new matter.

10-11. Claims 8, 15, 18, and 21-22 stand rejected under 35 USC 112, first paragraph for alleged lack of written description. The Examiner says the description in the specification of a bioreactor used in the synthesis of oligonucleotides or peptides does not provide an adequate representation of the claimed apparatus in which any polymer is attached or linked to the substrate. The Examiner says the specification disclosure is specific to the synthesis of oligonucleotide or polypeptide arrays on a solid support using photolithographic techniques. The Examiner also cites *University of California v. Eli Lilly* for the proposition that written description of an invention involving a chemical genus requires a precise definition such as by structure formula or chemical name. The Examiner also says that methods of making polymers such as carbohydrates or lipids were not known at the time of invention.

Initially, it is noted that the rejection is not applied to claims 9 and 10 directed to polypeptides and nucleic acids. Thus, the basis of the rejection appears to be directed to the additional breadth in claim polymers vis a vis polypeptides and nucleic acids. The rejection raises a number of issues which will be addressed in turn.

Further, the specification does describe the preparation of a large variety of polymers in addition to polypeptides and nucleic acids (see p. 21, lines 4-16). Thus, the issue with respect to claiming polymers more broadly than nucleic acids and polypeptides cannot be one of new matter.

In some circumstances, as in the *Lilly* case, the Federal Circuit has found lack of written description for reasons other than new matter. However, the cases in which this has occurred have principally, if not exclusively, involved newly isolated nucleic acids. For example, in *Lilly*, the court held that a claim directed to nucleic acids encoding human insulin (a hitherto uncloned human protein) lacked written description in the absence of actual sequence data for a nucleic acid encoding human insulin. The *Lilly* court also found that generic claims to cDNA encoding vertebrate or mammalian insulin lacked written description because:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more is not an adequate written description of the genus because it does not distinguish the claimed genus form others, except by function. It does not specifically define any of the genes that fall within its definitions. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated does not suffice to define the genus because it is only an indication of that the gene does, rather than what it is. 43 USPQ2d at 1406.

The facts and circumstances of the present claims are different than those in the *Lilly* case. In the *Lilly* case, the alleged invention resided in a novel DNA described only by a functional property. The structural feature of DNA per se was not sufficient to distinguish the claimed invention from other types of DNA. Here, the claimed invention does not lie in newly isolated polymer sequences, but rather in the combination of polymers with an apparatus having the various structural features recited in the present claims. The structural features of the apparatus in combination with the generic structural feature of the polymers within the apparatus are sufficient to distinguish the present claims from any prior art. Thus, applicants

have described the claimed invention with structural features not commonly possessed by other types of apparatus, satisfying the written description requirement.

Finally, the Examiner raises issues of how polymers other than peptides and nucleic acids can be made and linked to a solid support. Although raised as a matter of written description, the substance of this rejection appears essentially the same as the lack of enablement rejection below. Thus, applicants respond in the same manner.

12. Claims 8, 15, 18, 21-22 stand rejected under 35 USC 112, first paragraph on the basis that the specification although enabling for peptides and oligonucleotides is not enabled for other polymers. The Examiner says that the specification does not teach the manner of linkage of polymers to a support, and that the linkage is unique to the polymers and the substrate used. The Examiner says the working examples are limited to oligonucleotide and polypeptide synthesis. The Examiner says the claims are open ended regarding the linkage or attachment of polymers other than oligonucleotides to a support, and the reaction conditions and the order of the deprotection reaction.

Initially, it is noted that the rejection is not applied to claims 9 and 10 directed to polypeptides and nucleic acids. Thus, the basis of the rejection appears to be directed to the additional breadth in claim polymers vis a vis polypeptides and nucleic acids.

In fact, it is not correct that every polymer requires a unique manner of linkage to the support. Polymers can be linked through common functional groups such as amino, hydroxyl, carboxyl or thiol with complementary functionalities on a support. For example, the specification discloses that amino acids can be linked through carboxy or amino functional groups (p. 97, lines 4, 13), and nucleotides, carbohydrates and sugars via hydroxyl functional groups (p. 97, lines 5 and 14). Hydroxy, carboxy and amino groups can also be used as a complementary functional group on the substrate (see specification at p. 29, lines 15-16). The identification of such common functional groups and complementary reactive groups was a matter of routine organic chemistry.

[redacted]

The principles for synthesizing polypeptides and nucleic acids can readily be extended to synthesis of other polymers. In the general case, polymer are synthesized from monomers having two functional groups that support chain elongation. A first group allows the monomer to attach to a growing chain of a polymer. A second group allows the monomer after incorporation into a polymer to attach to the next monomer to be incorporated. Such a synthetic scheme can be adapted to photochemical synthesis by protecting the second group with a photosensitive protective group. For example, Cho et al., Science 261, 1303-5 (1993) describe use of a photodeprotection strategy to synthesize an array of oligocarbamates substituted with a variety of side chain in accordance with the teaching of the present application. The polymers were synthesized from nitrophenyl carbonate monomers bearing a photosensitive protecting group on a terminal amino moiety. Synthesis proceeded by photodeprotection of the amino group on an immobilized growing chain allowing coupling of an incoming protected oligocarbamate. The photoprotecting group was NVOC as described in the present application.

As is noted in the specification, there are many other classes of compounds that can be synthesized in a component-by-component fashion, such as polysaccharides, polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyetheneimines, polyarylene sulfides, polysiloxanes, polyimides, and polyacetates. For example, to synthesize polyureas, a support functionalized with an amino group having a radiation-sensitive protecting group can be deprotected and treated with a monomer having a first functional group that is an isocyanate and a second functional group that is an amine, protected with a radiation sensitive protecting group. The tethered amine reacts with the isocyanate on the incoming monomer to form a urea linkage. The tethered monomer can then be deprotected to free the amine functional group that is then free to react with another monomer having an isocyanate and a protected amine thus synthesizing a polyurea.

In a related manner, to synthesize polycarbonates, a tethered hydroxy group having a radiation-sensitive protecting group can be deprotected and treated with an activating group (e.g., phosgene or a phosgene equivalent) followed by a monomer having a first functional group that is a hydroxy group and a second functional group that is a hydroxy, protected with a

radiation sensitive protecting group. The tethered monomer can then be deprotected to liberate or make available the hydroxy functional group that is then free to be activated and react with another monomer having a hydroxy group and a protected hydroxy group. In such a stepwise fashion, a polycarbonate can be constructed.

Synthesis of polyamides can proceed in the same manner as is used for peptide construction. In particular, each monomer will have a first carboxylic acid functional group and a second amine, protected with a radiation sensitive protecting group.

These examples illustrate that the principle of using a radiation-sensitive protecting group to protect a functional group on incoming components and selectively removing such functional groups by directing radiation to known locations of a substrate is generally applicable to many classes of polymers.

The specification also describes an alternative embodiment in which preformed polymers are attached to a substrate (see pp. 126-128). In this embodiment, the substrate is coated with caged binding members, that is, a member whose affinity to bind a partner moiety is masked by a protecting group. The methods work by removing the protecting group from selected locations on the substrate and contacting the substrate with the polymer desired to be bound to the substrate linked to a partner moiety to the binding member. The polymer attaches through binding of the partner moiety to the binding member. The process can be repeated to attach additional types of polymer. In this method, the same binding member and partner moiety can be used for different types of polymer. Again, selecting a suitable reactive group, such as amino, hydroxyl, carboxy, or thiol to attach the partner moiety to a polymer is a matter of routine organic chemistry.

With respect to the Examiner's comments regarding the claims not reciting how polymers are linked, reaction conditions and deprotection steps, it is noted that the claims are product claims not method claims. It is not necessary to recite method of production steps in a product claim or otherwise to limit a product claim to a preferred method of production.

For these reasons, withdrawal of the rejection is respectfully requested.

13-14. Claims 8-22 stand rejected under 35 USC 112, second paragraph for reciting the term "about." This term has been deleted.

15-16. The claims stand rejected as obvious over reactor discussed by Urdea. The Examiner acknowledges that the claimed invention differs from Urdea's reactor in the recital of the depth of the cavity and that the substrate seals the cavity. However, the Examiner takes the view that loosely packed solid supports in Urdea's reactor contact porous barriers at the ends of the reactor, thereby indirectly sealing the reactor. The Examiner also says that Urdea teaches that the reactor has a minimum volume to reduce the usage of the reagents and that the dimensions of the reactor are not critical. Thus, the Examiner says it would be obvious to use a smaller reactor for the benefit that a small volume of reactants can be used. This rejection is respectfully traversed.

Initially, it is noted that essentially the same rejection was raised in the parent case and ultimately withdrawn. The present claims are distinguished for the at least the same reasons, namely, Urdea does not disclose or suggest a reactor in which a substrate is mated to and seals a cavity in the reactor, nor a reactor having a depth less than 1000 microns.

In the present case, the Examiner proposes a new theory by which the particles in Urdea reactor are alleged to seal the reactor. That is, the particles come into contact with porous barriers at the end of the reactor. However, the porous barriers at the ends of Urdea's reactor serve as inlet and outlets for introduction and removal of fluid. The barriers are sufficiently fine to retain the particles yet sufficiently porous to allow introduction and removal of liquids (col. 5, lines 8-12). Although the particles in Urdea's reactor may come into contact with the porous barriers as the particles are agitated in the chamber, the contact is only transitory and does not seal the barriers so as to prevent the entry or egress of fluids. If the contact did seal the barriers, then there would be no way of introducing or eliminating fluids from the reactor, thus defeating the purpose of having porous barriers and rendering the reactor inoperable.

[redacted]

Further, it would not have been obvious to miniaturize Urdea's reactor such that the reactor chamber has a depth of less than 1000 microns. Urdea's reactor uses multiple particles each of which is 100-180 μm in size. The aggregate size of the particles imposes an absolute limit to miniaturization. Further, the dimension of Urdea's reactor has to be significantly larger than the sum of multiple particles to allow the particles to be dispersed and agitated in the reactor chamber. Each of such dimensional requirements of Urdea's reactor presents a barrier to further miniaturization.

Although Urdea does refer to minimizing reactor volume to save reagents, this statement is immediately followed by the statement that the length of the Urdea et al. reactor is usually "*at least* 1 cm with no upper limit, usually being from 1.0 cm to 25 cm" (col. 4, lines 64-66, emphasis supplied). Any economy achieved by saving reagents is obviously a subordinate consideration to ensuring that polymer synthesis can occur. The reaction chamber cannot be reduced in size to a point that would not allow enough room for dispersion and agitation of particles. By indicating that the reaction chamber should be at least 1 cm deep immediately following his comments regarding saving reagents, Urdea conveys to the reader that miniaturization should not go beyond about 1 cm. This is at least ten fold larger than the depth of the claimed apparatus.

For these reasons, withdrawal of the rejection is respectfully requested.

17-18. The claims stand rejected for alleged double patenting over commonly owned US 6,420,169. Applicants **attach** a terminal disclaimer to moot the rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Appendix